Introduction to Bio-inspiration and Lab-On-a-Chip system:

仿生與實驗室晶片導論

An-Bang Wang

王安邦

國立臺灣大學 應用力學研究所

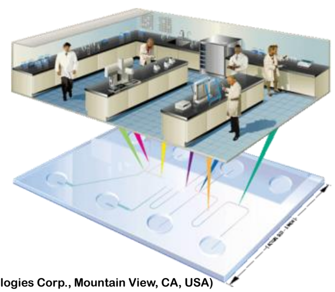
Institute of Applied Mechanics, National Taiwan University

What is Bio-inspiration?

- **Bioinspiration** is the development of new things inspired by observations/solutions in **nature**.
- Bioinspiration vs. biomimicry/biomimetics
  the latter aims to precisely replicate the designs of biological materials. Bioinspired research is a return to the classical origins of science: it is a field based on observing the remarkable functions that characterize living organisms, and trying to abstract and imitate those functions. (Wikipidia)

What is Lab on a chip ?

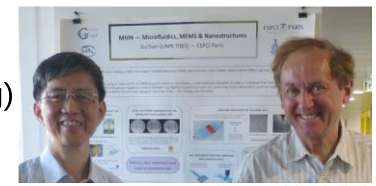
LOAC (or LOC): **combining different operations**, which are originally performed in laboratories, **in a single microdevice**. (Berthier & Silberzan)



(From: Caliper Technologies Corp., Mountain View, CA, USA)

What are *LOAC & μ-fluidics*?

- *There are different names used in the literature:* ***μ-fluidic,*** *MEMS-fluidics,* ***LOAC,*** *μ-TAS* (*TAS*: **T**otal **A**nalysis **S**ystems)*, BioMEMS, biochip, nanofluidics, nanoflows… etc.*
- ***μ-fluidic*** is the study of flows, which are circulating in artificial *μ*-systems. (Prof. **Patrick Tabeling**)



(Prof. Patrick Tabeling)

Lecturers

- 王安邦　臺大應用力學研究所、醫療器材與醫學影像研究所特聘教授
- 林致廷　臺大電機工程學系教授、奈米機電系統研究中心主任
- 林順區　臺大奈米機電系統研究中心辦公室主任
- 侯詠德　臺大生物產業機電工程學系助理教授
- 黃念祖　臺大電機工程學系生醫電資所副教授
- 陳建甫　臺大應用力學研究所副教授
- 楊鏡堂　臺大機械系終身特聘教授
- 蘇剛毅　臺大醫學檢驗暨生物技術學系副教授

Course Organization (I)

實驗室晶片(Lab-on-a-Chip)系統是**將原本在實驗室不同階段之操作流程整合並微小化在一片晶片系統上**。利用這種技術，醫生在幾分鐘的問診過程中可同時**快速診斷**出病人的疾病，並對症下藥；生化實驗可以減少人因干擾、**避免**人員直接曝露於有害試劑的**危險工作**；另外，實驗室晶片因具有可**自動化與平行化操作處理**的特色，所以可用於快速篩選或合成新藥與產品，並**增加實驗的可信賴度**；而由於在晶片上僅需極少量的試劑且具表面體積比增大之優點，更可**大幅減少試劑用量、減低操作成本及縮短操作處理時間**。目前已有越來越多的實驗改在實驗室晶片上進行，例如血液分離、電泳分離、聚合脢鏈鎖反應（PCR）、核酸的定序反應分析等等，而拋棄式的塑膠晶片也有漸成設計主流之趨勢。

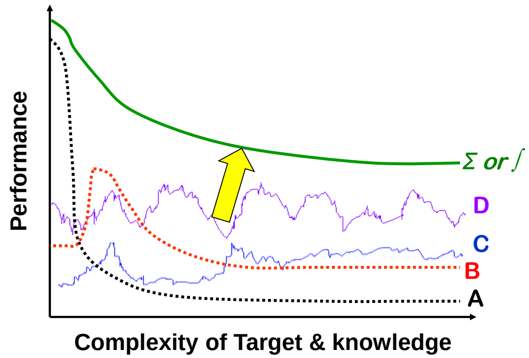
Course Organization (II)

- 從大自然可以領略更多的靈感，所以本課程也將介紹相關**仿生案例**，讓同學可以多體會大自然的奧祕、並觸類旁通，以幫助實驗專題設計與執行。
- 課程設計上，這是一門結合「自然與工程」、「理論與實作」和「研究與應用」六合一的實際動手參與，以完成不同**實驗專題**的應用導向之工程與實作多樣學習課程。
- 第**5**、**10**週將安排在臺大奈米機電系統研究中心無塵室實習；第**16**週將安排在醫學院醫學檢驗暨生物技術學系上課，並參觀臺大基因體中心。

Course Organization (III)

- 在課程中，將讓同學到實驗室動手製做，讓同學們**結合不同專業組成跨領域團隊(每隊1-3人)，以實際動手完成不同的實驗專題**，訓練同學們以**目標為導向**之**團隊合作與邏輯推理能力，同時開啟未來可能之研究方向**。
- Language: Chinese; lecture notes mainly in English
- Lecture Notes on Web: (http://bernoulli.iam.ntu.edu.tw)
- Grading Policy: Class participation (10%); 1st & 2nd Mid-term project presentation (15 + 15%); Final oral & written report of term project (30%+30%)

Why interdisciplinary?



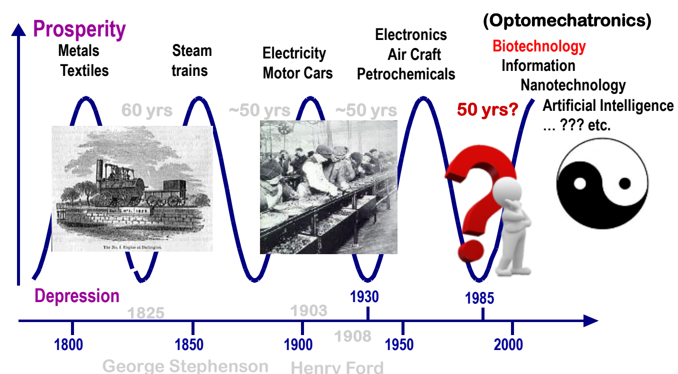
Course Contents (I)

1. Introduction to LOC仿生&實驗室晶片導論及議題設計介紹
2. Introduction to Biomimetics 仿生學簡介 (I)
3. LOC & Term project assignment
   實驗室晶片導論與實驗室晶片議題分配
4. 肝臟與肝臟晶片技術簡介、應用與未來展望
5. General fabrication techniques
   微製程技術簡介 & 實作(I) : MEMS實作篇(A)
6. Introduction to Biomimetics 仿生學簡介 (II)
7. Microfluidics for bio-sample pretreatment
   用於生物樣本前處理之微流道系統
8. Introduction to Optofluidics 光流體系統簡介
9. 1st Mid-term project presentation & lab course
   第一次期中報告與實驗室分組實作

Course Contents (II)

10. Lab course 實驗室晶片設計與實作(II): MEMS實作篇(B)
11. Design of micro-reactors and its application
    微流體混合/反應暨生醫化材應用
12. Polymer-based microfluidic sensors 塑基微流體感測器
13. Paper-based microfluidic sensors 紙基微流體感測器
14. 2nd Mid-term project presentation
    第二次期中討論與報告
15. Electronics-based bio-sensing technologies
    生醫電子感測元件
16. 醫學分子檢驗新技術 (& Lab course)
17. Transport phenomena of droplets and lab-on-a chip
    液珠輸送與檢測晶片
18. Final report 期末報告

Trend of the world



Can the nature guide us the way of change?

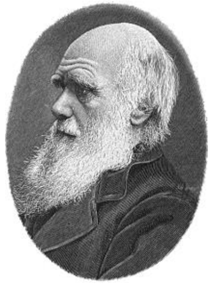
Who can survive in the changing world?

- The one that is the strongest
- The one that is the most intelligent
- The one that is most active
- The one that works very hard
- The one that is most modern
- The one that is most rich
- …

A Simple Answer

It is **not** the ***strongest*** of the species that survives, **nor** the **most intelligent** that survives.

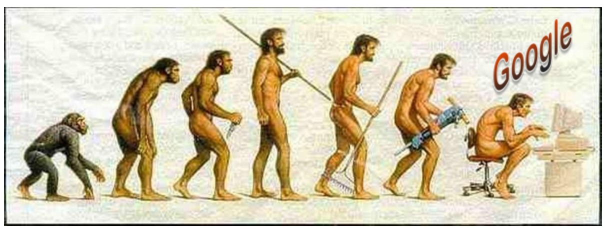
It is the one that is the **most adaptable to change**.



Charles Darwin
(1809~1882)

That's it?

- **Another answer?**
- Converging or diverging trend?
- Related effect: lower/higher entrance barrier?



https://evblog.virginiahumanities.org/2012/05/the-kkk-and-evolution-in-virginia/

"Adaptable to change"

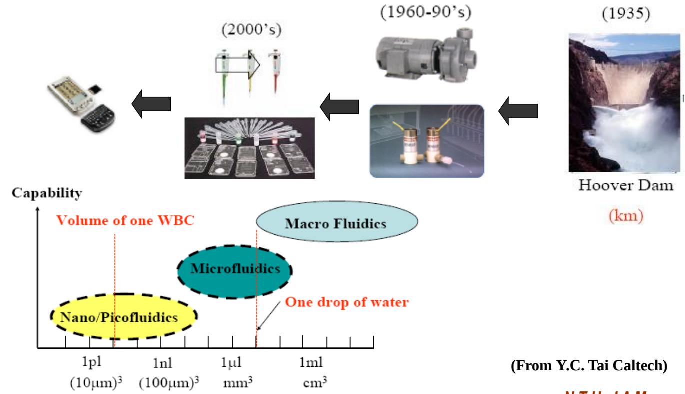
- What can the "change" bring (for you)?
  Can you waive the "change"?
- "Change" vs. "Novelty"
  Keep changing from the same to be different
- What is/are the key parameter(s) of "**adaptable to change**"?
  Learning from the nature (Biomimetic).
- What is/are the key(s) of "change" that related to us (**students / professors**)?

What is Microfluidic technology

- **Fluidic:** manipulating (or control) fluids
- **Microfluidic = "Micro" + "Fluidic"**

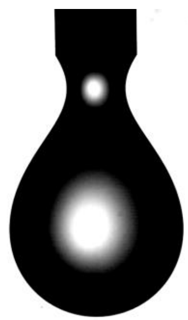
Coanda effect

From Fluidic to Microfluidic technology



(From Y.C. Tai Caltech)

Is it a microfluidic device?



1. Yes
2. No

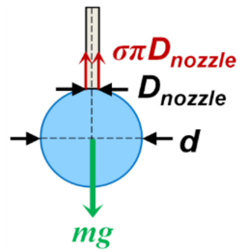
*Microfluidics is **not** so far from our life!*

Prediction models for dripping drop sizes (I)

Tate (1864)

$$F_\sigma = F_g$$

$$\sigma\left(\pi D_{nozzle}\right) = mg = \rho\left(\frac{1}{6}\pi d^3\right)g$$



$$\Rightarrow \left(\frac{d}{\lambda}\right) = \left(\frac{6D_{nozzle}}{\lambda}\right)^{1/3}, \text{where } \lambda \equiv \sqrt{\frac{\sigma}{\rho g}}$$

σ : Surface tension of liquid

ρ : Density of liquid drop

g : Gravitational acceleration

D_{nozzle} : Diameter of nozzle

$$d^* = 1.82\left(D^*_{nozzle}\right)^{1/3}$$

Prediction models for dripping drop sizes (II)

Yildirim, Xu & Basaran (2005)

(simulation: $We \leq 10^{-5}$ & $Oh \leq 1$) $We = \frac{16\rho Q^2}{\pi^2 \sigma D_{nozzle}^3}$ $Oh = \frac{\mu_d}{\sqrt{\rho \sigma D_{nozzle}}}$

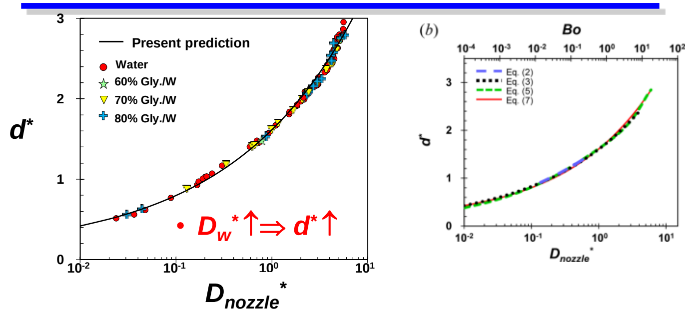
$$d^* = 1.61\left(D_{nozzle}^*\right)^{0.288}$$

What should be the characteristic length D_{nozzle}?

Subtle difference can make significant difference in Microfluidics!

Tsai & Wang, **Langmuir** (2019), 35, 4763−4775.

Prediction models for dripping drop sizes (III)



- ***All data*** **can be well-predicted by a single parameter D_w^* in the whole range by** $d^* = 1.51 D_w^{*1/3} + 0.10$

How to precisely metering in biomedical lab?

What is a microfluidic platform?

- It's a toolbox …
  - containing a reduced number of building blocks
  - for a dedicated set of microfluidic operations
  - that can easily be combined
  - within a well defined (low cost) fabrication technology
- The platform concept is not new …
  - type setting in book printing ("Gutenberg bible")
  - computer industry
  - automotive industry

(Zengerle & Haeberle)

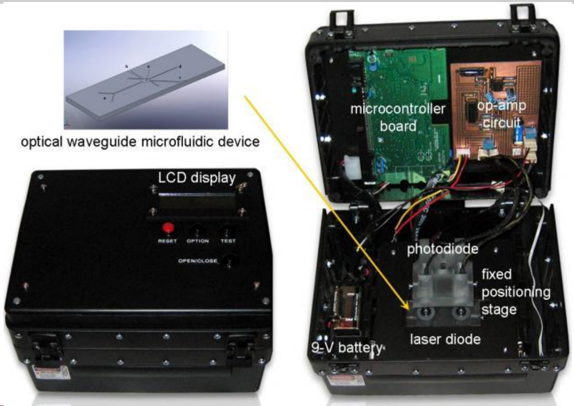
The Trend of Industry

The trend of industry development depends on the trend of human needs.

- ***Providing Ubiquitous Total solution***
- ***Integration of functionality***
- ***Built in precision/inspection/automation***
- ***Reduce time to certification/ (mass) production /market /profit***

(程一麟)

A Lab-on-a-chip system example



Microfludic Platform @ AB WANG's Lab

Microfluidic components

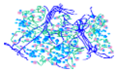
- Microvalve
- Micropump
- Micromixer
- **Microdistributor/ coater**
- Microflowmeter

Integrated microfluidic systems & Applications

- **Micro-squential control system**
- Micro- reactor / emulsion system for novel materials
- Compact Pattern Coating System
- **Compact Desktop Coating System**
- **Micro-liter POCT analysis system**
- Biomedical μm/nm 3D Printing system
- On-line Coating Film Measuring System
- Long-period Drug-delivery & Monitoring System

What are Fluids?

- **Fluid** is a substance tending to flow or conform to the outline of its container (*Merriam-Webster's Collegiate Dictionary,* Static aspect)
  Fluids are the substance that **could not resist deformation,** move and deform continuously under the application of a shear (tangential) stress, no matter how small the shear stress may be. (*F. White,* Dynamic aspect)
- **Fluids include**
  - **Liquid**: a state of matter in which the molecules are relatively free to change the positions w.r.t. each other but restricted by cohesive forces so as to maintain a relatively fixed volume.
  - **Gas**: a state of matter in which the molecules are practically unrestricted of cohesive forces and has neither definite shape nor volume.
- **Some systems contain complex phenomena, like a group of solid that shows the ability to flow and polymers resist deformation etc.**



www.chemistry.helsinki.fi

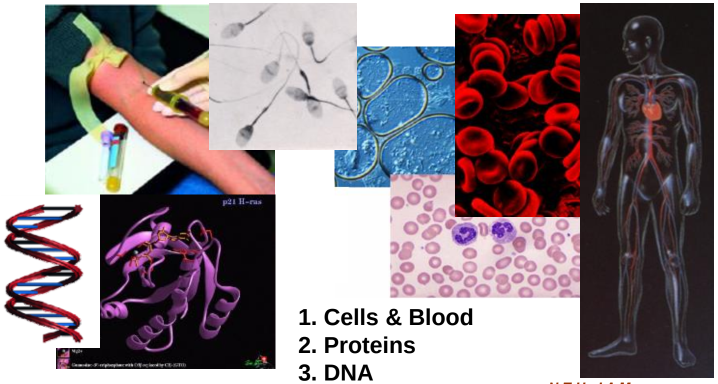
Polymers as frozen liquid

sand as a liquid

Why liquids?

- About 70% of the Earth is covered with water, and 97% of that is the salty oceans.
- The human body is 72% saline (salt) water.
- A significant fraction of the human body is water. This **body water** is distributed in different compartments in the body. Lean muscle tissue contains about 75% water. Blood contains 83% water, body fat contains 25% water and bone has 22% water (Wikipedia).

Biological Fluids



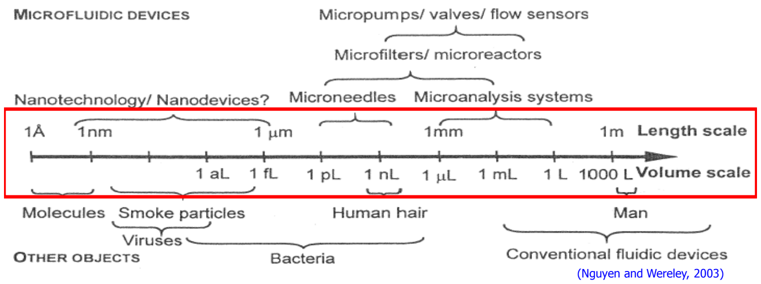
1. Cells & Blood
2. Proteins
3. DNA

Issues in the biomedical applications

- Sample
- Contamination
- Accuracy
- SOP
- Automation
- Timing of Sequence
- Cost
- Space

Length scale & Volume scale

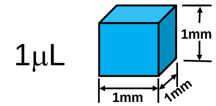
◆ ***Feeling is important***

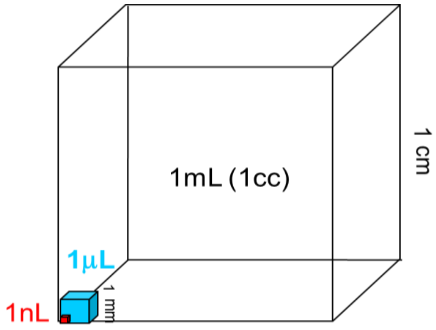


How big is a drop size from a eyedropper?

1. 5000
2. 500
3. 50
4. 5
5. 0.5

(unit: µL)





Why microfluidic technology?

Issues in Biomedical Industry:

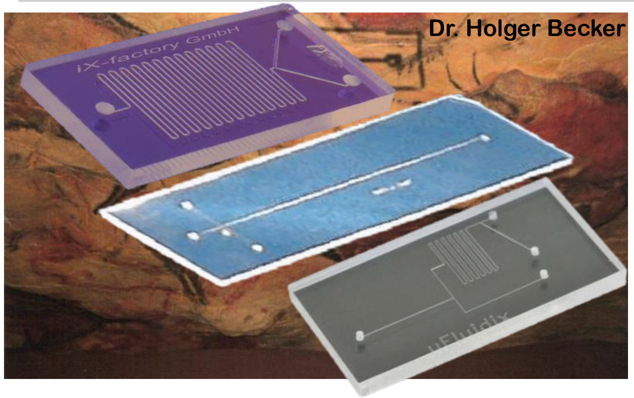
- Constant need of novelty and cost down
  - ⇒ New challenges in manufacturing technology

Advantages of microfluidic technology:

◆ Short diffusion time ($t_D \propto L^2$)
◆ High Surface/Volume ratio ($\propto 1/L$)
  ⇒ better mass & heat transfer
◆ Less samples and fluid consumptions
◆ Short operation time
◆ Well-controlled micro-environment
  ⇒ Parallel operation ⇒ Easy scale up
◆ Automation & Portability

Reduce overall costs

Microfluidic has been around for a long time?



Introduction to Surface Tension

Surface tension is the force applied along the interface of two immiscible fluids per unit length.

Surface tension is the tendency of liquid surfaces to shrink into the minimum surface area possible. (From Wikipedia)

Surface tension is the energy required to increase the interface of two immiscible fluids by an unit area.

http://itsforyourlife.com/

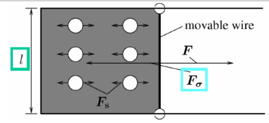
http://www.liv.ac.uk/

http://fphoto.photoshelter.com/

http://www.natoco.co.jp/

Surface Tension & Surface Energy

- Definition $\sigma = \frac{F_\sigma}{l}$

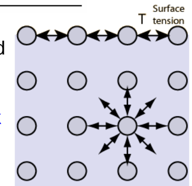


Surface tension: Force per unit length [N/m]

- The term „tension“ is bad choice (Commonly referred to as force per **area)**
- Microscopical Phenomenon relates to
  - Energy required to **transport molecule** from **bulk** to **surface** region
- More physical definition of surface tension:

Surface Energy: Energy needed to extend surface

$$W = F_\sigma dx = 2\sigma\, l\, dx$$

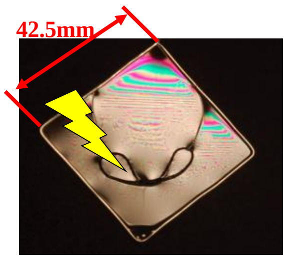


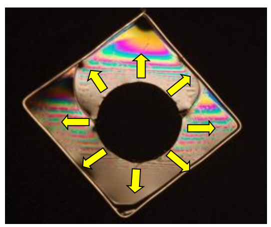
hyperphysics.phy-astr.gsu.edu/hbase/surten.html

- **Systems always search to minimize Energy = minimize Surface/Interface (with highest Energy)**

(Ducrée and Zengerle)

A experiment of Surface tension: Soap-film

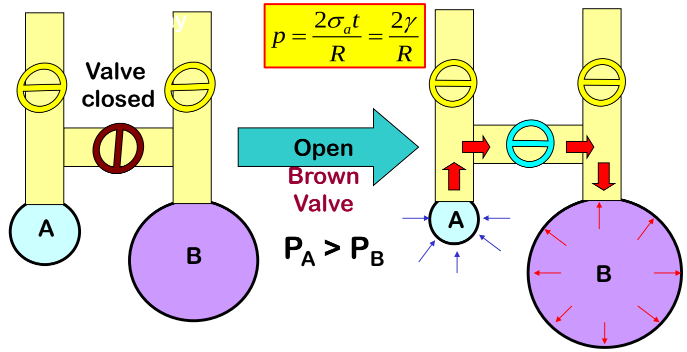




- Circle has **maximum surface** for a **given periphery**
- Surface tension reduces surface energy to be minimum
- Try to think about the liquid shape of different drop sizes

Surface tension vs. Pressure Soap-film Mechanics

$$p = \frac{2\sigma_a t}{R} = \frac{2\gamma}{R}$$



How to use liquid surface tension to transfer liquid?

- In macroscopic systems, we use pumps (positive pressure drop) to transfer liquid
- In microfluidic system, negative pressure drop, i.e., suction, is frequently used.
- Typical example is the Lateral Flow Assay (LFA) used in the point-of-care test (POCT).

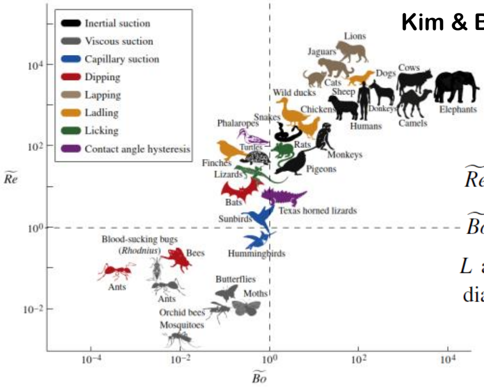
The mosquito strategy for eliminating dengue

- Periodic outbreaks of dengue — a disease that affects nearly 400 million people annually worldwide and kills 25,000.
- Distinguishing vs. Farming
- ***Wolbachia*** technique: releasing mosquitoes modified to carry a bacterium called *Wolbachia*, which stops the insects from transmitting some viruses, led to a steep drop in cases of dengue fever since the 1990s. (Nature/NEWS/2020/8/27)

Natural Drinking Strategies

- Drinking is critical in the sustenance of most animals. Not only water, many insects and birds ingest fluid primarily in the form of nectar. Classification according to the principal force involved. (Kim & Bush, 2012 JFM)
- Suction is the most common strategy by through an orifice (e.g. lips or a beak) or a tube (e.g. a proboscis or a trunk) or by entrainment onto the tongue.

Global trend of drinking for animals



Kim & Bush, 2012 JFM

$\widetilde{Re} = (\rho u L/\mu)(L/H)$

$\widetilde{Bo} = \rho g H L/\sigma$

L and H are the tube diameter and height

Drinking Strategies – Suction

For active suction

ΔP -> independent of scale and so to be of comparable magnitude for all creatures.
ΔP ~ 10 kPa for mosquitoes, humans and elephants.
highest ΔP appears to be 80 kPa for bed bugs.

The tube diameter d should be 10 μm below which capillary pressure dominates the applied suction pressure.

For most creatures, the tube or mouth diameter d is significantly larger than 10 μm, so the capillary pressure is negligible. (mosquitos -> 100 μm) *Exception: hummingbird, zebra finch.

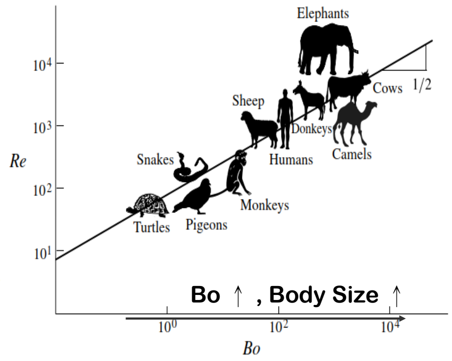
The tube height h should be 1m below which the applied suction pressure dominates hydrostatic pressure. -> gravity is negligible.

Law of Drinking Strategies – Inertia Suction

$$(Re(h/d) \gg 1)$$

$$Re = \frac{\rho u d}{\mu} \sim \left(Bo\frac{\sigma \Delta P}{\mu^2 g}\right)^{1/2}$$

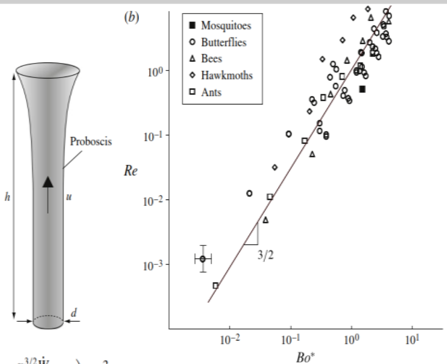
$$Bo = \rho g d^2/\sigma$$



Kim & Bush, 2012 JFM

Law of Drinking Strategies – Inertia Suction

$$(Re(h/d) \ll 1)$$



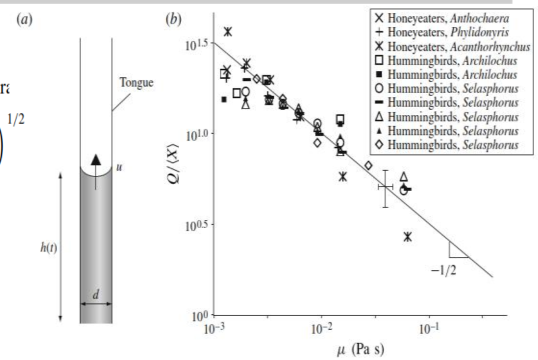
$$\log Re \sim \frac{3}{2}\left(\log Bo + \frac{2}{3}\log\frac{\sigma^{3/2}\dot{W}}{32\mu^2 h\rho^{1/2}g^{3/2}Q}\right) \equiv \frac{3}{2}\log Bo^*$$

Kim & Bush, 2012 JFM

Drinking Strategies – Capillary Suction

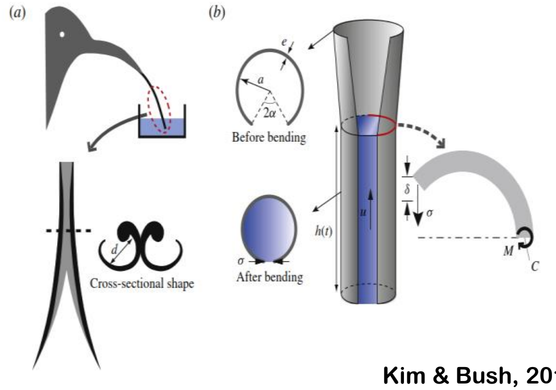
average volumetric flow ra

$$Q \sim \frac{\pi d^2}{4}\bar{u} \sim \left(\frac{\pi^2 d^5 f}{32\mu}\right)^{1/2}$$



Kim & Bush, 2012 JFM

Drinking Strategies – *Hummingbird's tongue*

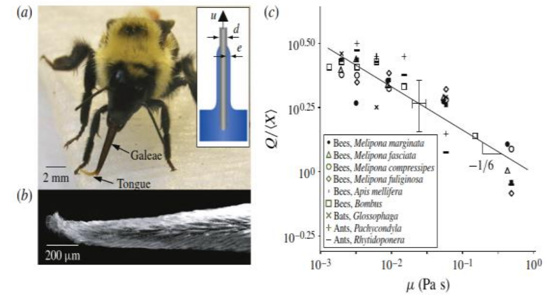


Kim & Bush, 2012 JFM

Drinking Strategies – *Viscous Dipping*

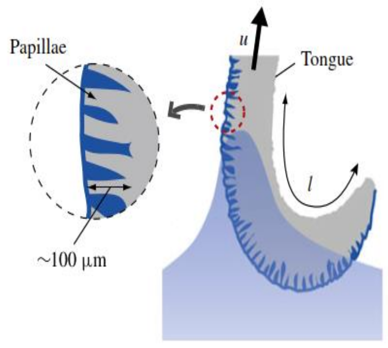
average volumetric flow rate

$$Q \sim \pi deu \sim \frac{\pi d^2 \dot{W}^{5/6}}{\sigma^{2/3} h^{5/6} \mu^{1/6}}$$



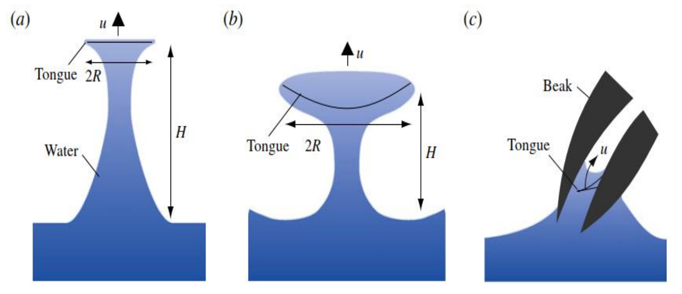
Kim & Bush, 2012 JFM

Drinking Strategies – *Licking*



Kim & Bush, 2012 JFM

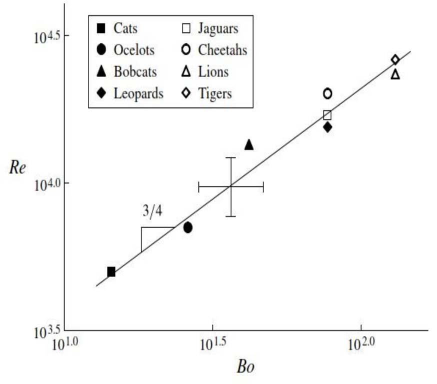
Drinking Strategies – *Inertial Entrainment*



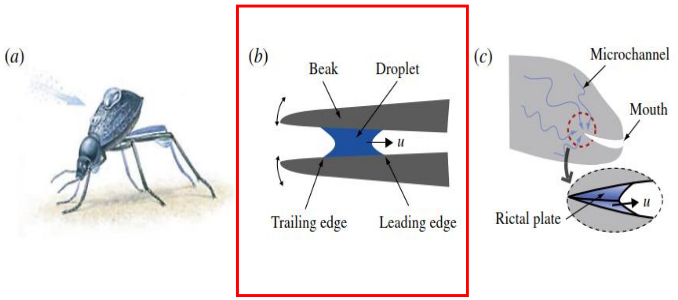
Kim & Bush, 2012 JFM

Drinking Strategies – Inertial Entrainment

$Re \sim Bo^{3/4}$



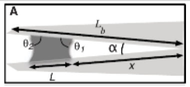
Drinking Strategies – Contact Angle Hysteresis

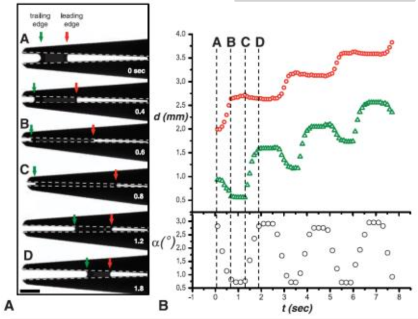


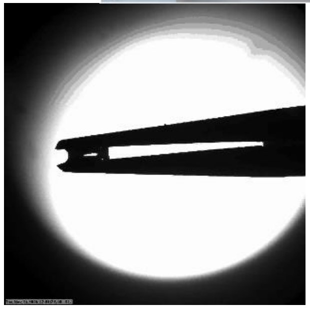
Kim & Bush, 2012 JFM

Capillary Ratchet (I)

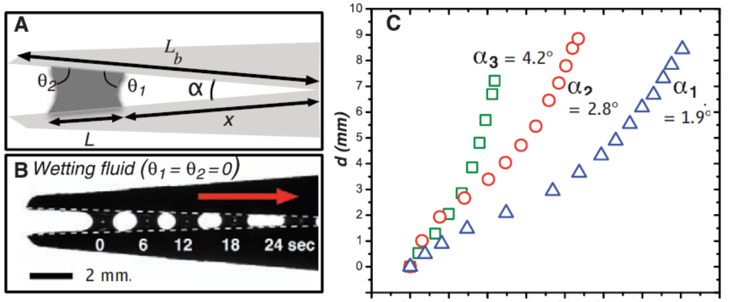
(Prakash, Quere, Bush, 2008, Science)







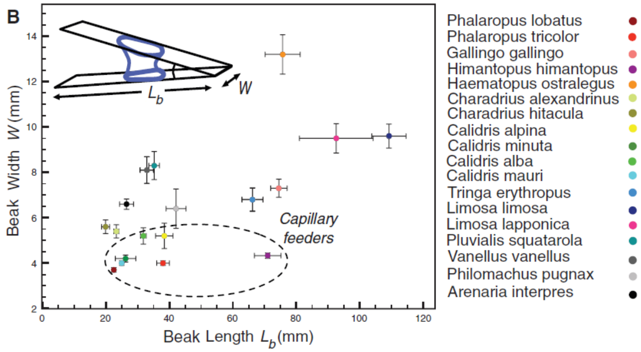
Capillary Ratchet (II)



silicone oil ($\theta_1 = \theta_2 = 0$, $\eta = 0.05$ kg m^{-1} s^{-2})

(Prakash, Quere, Bush, 2008, Science)

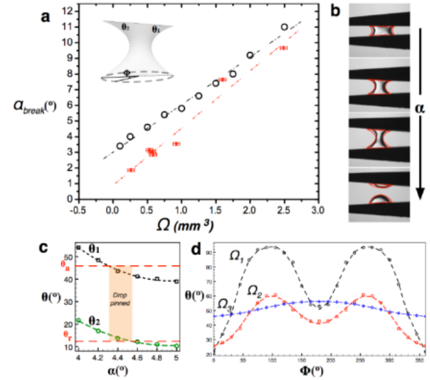
Capillary Ratchet (III)



(Prakash, Quere, Bush, 2008, Science)

Capillary Ratchet (IV)

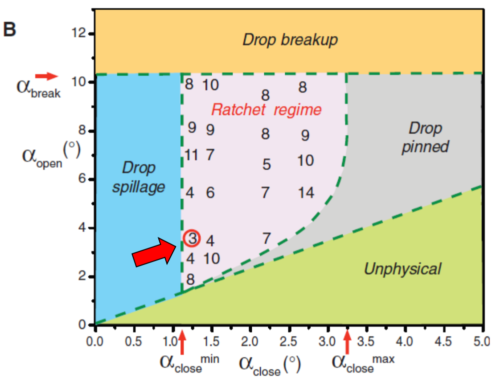
Key: Experiment + Simulation



(Prakash, Quere, Bush, 2008, Science)

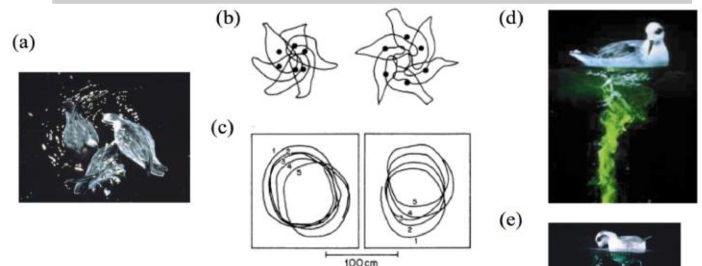
Capillary Ratchet (V)

Key: Mechanism + Map



(Prakash, Quere, Bush, 2008, Science)

Kinematics of Phalarope spinning (鷸)



Kinematics of phalarope spinning

Obst, et al., Nature, 384, 1996

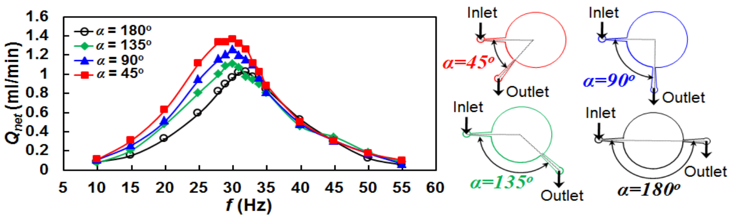
PHYSICAL REVIEW FLUIDS 2, 100507 (2017)

Seeking simplicity for the understanding of multiphase flows

Howard A. Stone

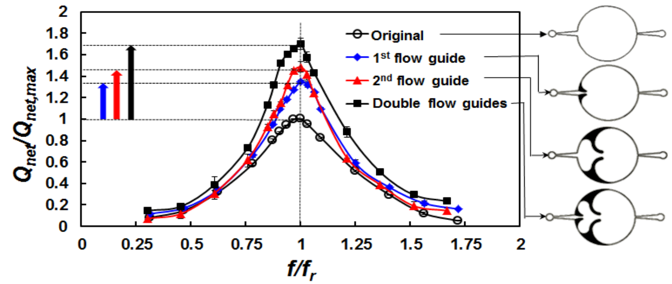
Development of Valveless Micropump

- Non-moving part valve (Valveless) instead of check valve
- The key component of Valveless Micropump
  - ✓ Rectifier(s) only ?
  - ✓ Vibration chamber is just a pressure source ?



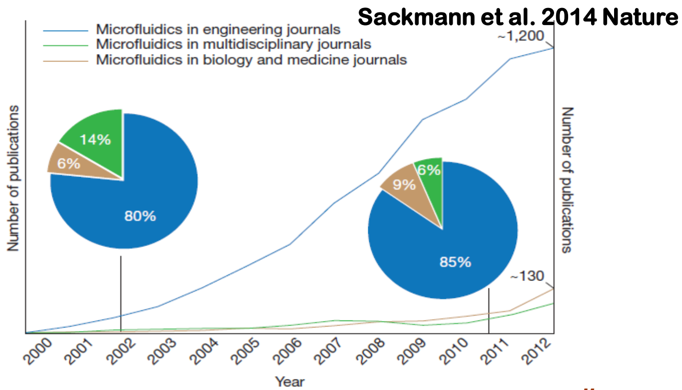
High-efficient μ-pump design inspired from nature

- Main concepts of Flow Guide (inspired from "Stone Weir"):
  - ✓ Reduce the reversal flow of inlet vortex pair
  - ✓ Enhance the forward flow of outlet vortex pair

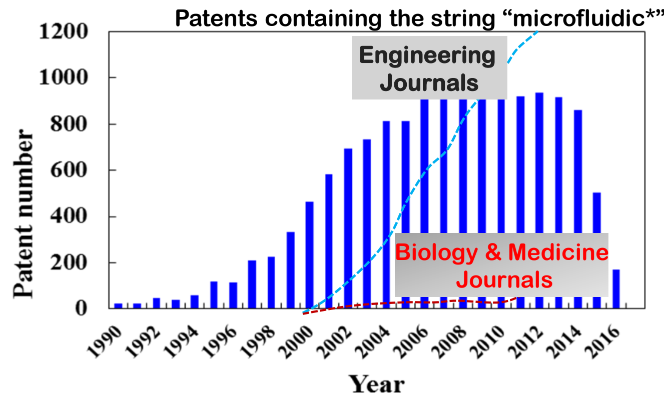


Wang & Hsieh, Lab chip, 2012, 12, 3024–3027

Microfluidics related Journal Papers



Annual granted microfluidic patents



Challenges & Strategy

Challenges:

- Proof-of-concept ≠ final product (Sackmann et al., 2014)
- Cool technology ≠ simple & cheap (Whitesides, 2013)
- Long path from Lab and producer to the end users
- Resistance due to "inertia" of experienced users (especially) in biomedical field

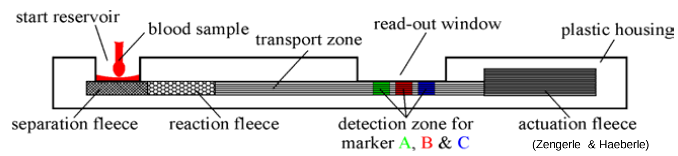
Strategy:

- ◆ Papers (for academy)? or Patents (for users/money)?
- ◆ Pioneer? or Better performance?
- ◆ Innovation design? or New system integration?
- ◆ Specific component/System or General method/device?

μ–Fluidics/LOAC for diagnostics

- ◆ There are many new designs for diagnostics

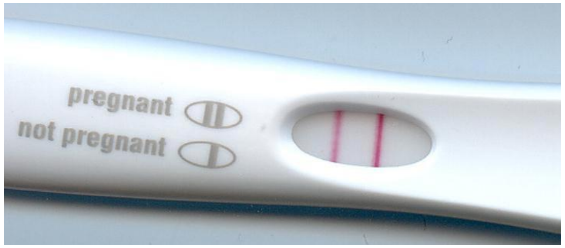
The **low-cost gold standard** the MEMS people and especially the Lab-on-a-Chip community have to compete with!



(Zengerle & Haeberle)

The pregnancy strip is a modern/traditional test ?

- ◆ Is the pregnancy strip a microfluidic device?
- ◆ The product became available in Canada **in 1971**
- ◆ This is a test of **hCG** (human chorionic gonadotropin)

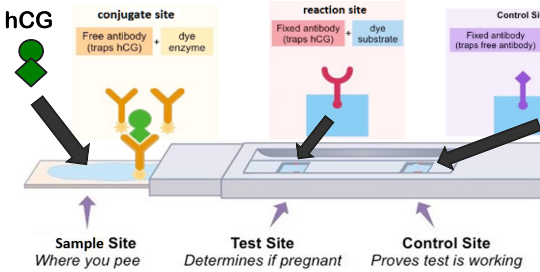


https://commons.wikimedia.org/w/index.php?curid=1815031

The sensor design of a lateral flow assay (LFA)

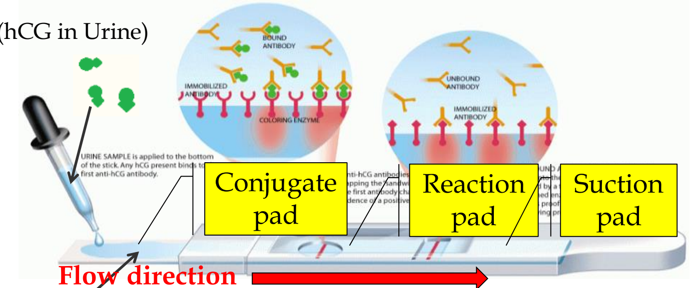
Low-cost example: pregnancy strip

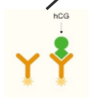
- ◆ Immunochromatographic assay (fast, simple-to-use)
- ◆ Terminology: Lateral Flow (LF) transportation



How a lateral flow assay works?

(hCG in Urine)





- Accuracy of LFA : 75 ~ 95%
- Accuracy > 99% ➩ confirmatory test

https://pregnancy.biz/pregnancy-tests/

Sensitivity and specificity

- **Sensitivity** (敏感性、有-陽性) measures the proportion of ***positives*** that are correctly identified (e.g.,真陽 the percentage of sick people who are correctly identified as having some illness).
- **Specificity** (特異性、無-陰性) measures the proportion of ***negatives*** that are correctly identified (e.g.,真陰 the percentage of healthy people who are correctly identified as not having some illness).
- It's a balance of "**trigger level**" setting.

http://www.padovar.com/safety-and-security/

Translated Products of Pregnancy Test

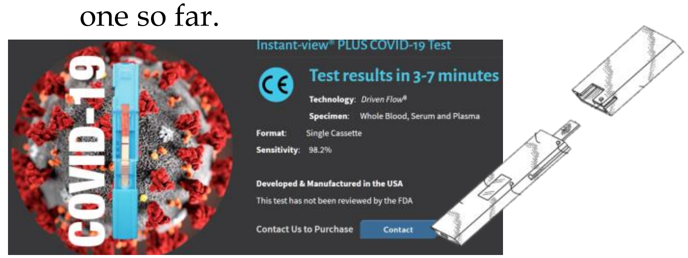
1. For Those Who are Trying to Conceive
2. For Those Who are Trying **NOT** to Conceive

1. **Which one needs higher sensitivity?**
2. **Which one can be expensive?**

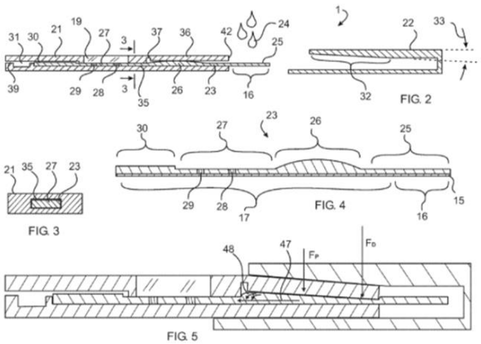
(瞿志豪)

Lateral flow assay

- Driven Flow® Technology, a new lateral flow assay (LFA) strip, claimed can finish test within 7 min. This looks to be a fastest one so far.



Lateral flow assay



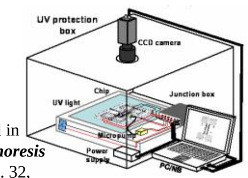
Will you join/invest such a startup?

- Yes, this is really cool!
- No. Why?
  Do the customers really care about the time reduction (from 10 min to 7 min) but cost increasing that you offered?

Examples of Past Term Projects

published in
Sensors and Actuators –B: Chemical, 2016, Vol. 222 pp. 721–727

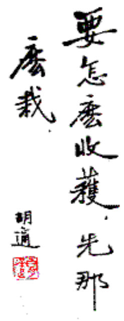
published in
Electrophoresis 2011, Vol. 32, p.423-430.



You can make it!

- 科技本乎人性(自然)
- 人有共通性，但沒有兩個人相同！
- 這個世界不能沒有你！

- 態度決定高度
- 細節決定品質
- 毅力決定成敗



Gravity-actuated Microfluidic Chip for Point-of-Care Urinary Creatinine Detection

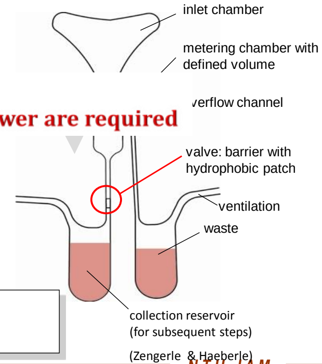
Sensors and Actuators –B: Chemical, 222 pp. 721–727, 2016

Centrifugal μ-Fluidics on Disk (I)

1. **liquid metering**
2. liquid switch
3. separation
4. mixing
5. detection

$$\boldsymbol{f}_{\nu} = -\varrho\boldsymbol{\omega} \times (\boldsymbol{\omega} \times \boldsymbol{r})$$

- **Patent issue**
- **Stable motor & power are required**

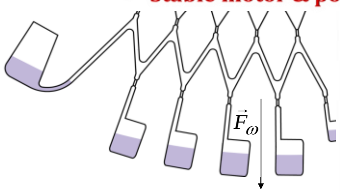


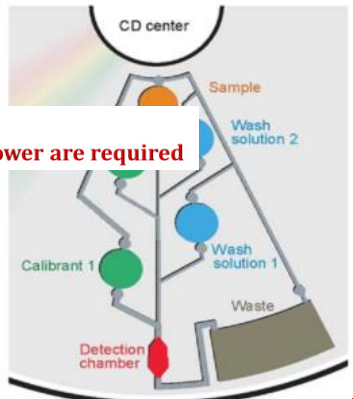
- Control by rotating speed
- Disposable & Low cost

Centrifugal μ-Fluidics on Disk (II)

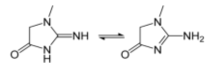
Splitting/Aliquoting for multi-channels

- **Patent issue**
- **Stable motor & power are required**





Target: Urinary Creatinine Assay (collaborated with NTU-Hospital)



Creatinine is produced at a fairly constant rate by muscle, and its concentration in blood or urine is a standard to evaluate the renal function.

Step 1: metering

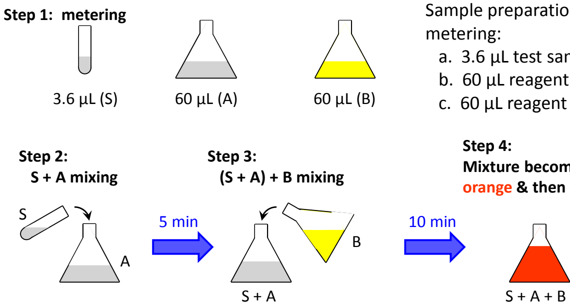
3.6 μL (S) 60 μL (A) 60 μL (B)

Sample preparation & precise metering:
a. 3.6 μL test sample (S)
b. 60 μL reagent A (A)
c. 60 μL reagent B (B)

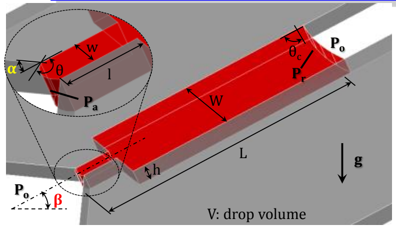
Step 2: **S + A mixing**

Step 3: **(S + A) + B mixing**

Step 4: **Mixture becomes reddish orange & then detection**



Capillary-Gravitational Valve



$$\Delta P_a = P_o - P_a = 2\sigma\left[\frac{\cos(\theta_c + \alpha)}{w} + \frac{\cos\theta_c}{h}\right]$$

$$\Delta P_r = P_r - P_o = -2\sigma\cos\theta_c\left(\frac{1}{w} + \frac{1}{h}\right)$$

$$\Delta P_g = \Delta P_a + \Delta P_r = -\rho g L \sin\beta$$

where $$L = \frac{\frac{V}{h} + (W - w)l}{W}$$

(Sensors and Actuators –B: Chemical, 222, pp. 721–727, 2016)

$$\beta_{op} = \sin^{-1}\left\{\frac{2\sigma W}{\rho g\left[\frac{V}{h} + (W - w)l\right]}\left[\frac{\cos\theta_c}{W} - \frac{\cos(\theta_c + \alpha)}{w}\right]\right\}$$

With an appropriate set of geometric design (α, w, W, h, and l), sequential control can be realized by simply changing β_{op}.

Lab-on-a-chip for point-of-care of Urine test

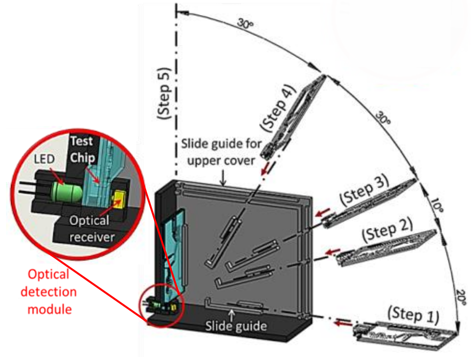
Step 5 : $\beta_{op} = 90^0$
Collection Mixture & Detecting

Step 4 : $\beta_{op} = 60^0$
Adding Reagent B and Mixing

Step 3 : $\beta_{op} = 30^0$
Adding Reagent A

Step 2 : $\beta_{op} = 20^0$
Metering Test Sample

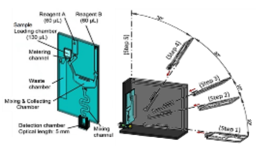
Step 1 : $\beta_{op} = 0^0$
Loading Test Sample

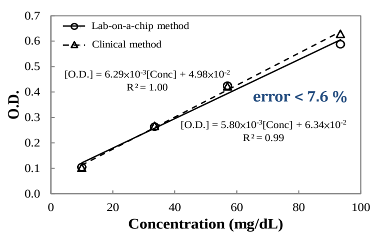


(TW Patent I446958)

Urine Chip vs. Clinical Method

Lab-on-a-chip method:





Clinical method:

(TBA-200FR, Toshiba)

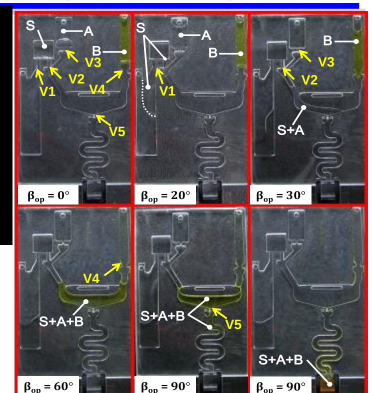
The new design is suitable for POCT (<10%) in remote areas even without electricity.

Sensors and Actuators –B: Chemical, 222 pp. 721–727, 2016

Functional Test of Urine-Chip

*The chip is placed on the rotating stage in the horizontal plane.

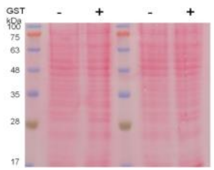
*Load reagent A , reagent B , and urine sample.



0°: load samples
20°: open **V1** (S precise metering)
30°: open **V2 & V3** (S + A)
60°: open **V4** (S + A + B)
90°: open **V5** (detecting)

A Novel DNA Selection and Direct Extraction (SDE) Process and its Application in DNA recombination

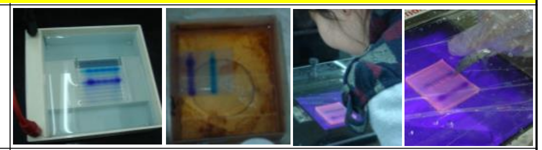
(Electrophoresis, 2011, 32, pp. 423–430)



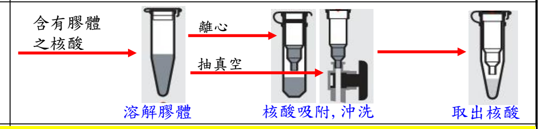
傳統實驗室DNA重組流程

減少操作時間？降低人力需求？

3. 膠體電泳 Electrophoresis ~ 1天



4. 核酸萃取 DNA Extraction montreal-biotech

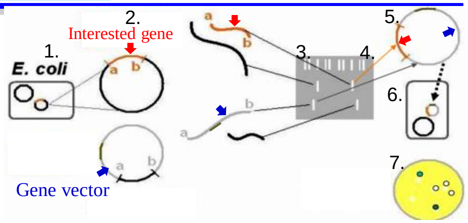


避免暴露於致癌物及紫外光環境？

DNA Recombination

Lab process

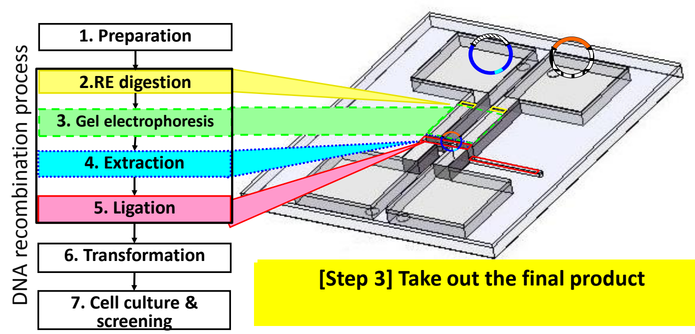
1. DNA preparation	(~1 hr)
2. RE digestion	(1~2 hr)
3. Gel electrophoresis	(~1 hr)
4. DNA extraction	(~1 hr)
5. DNA ligation	(1~20 hr)
6. Transformation	(1~2day)
7. Cell culture & selection	(~4 hr)



Demerits：

1. Low production rate
2. Time-consuming
3. Hard manipulation of large DNA
4. Exposure to dangers (EtBr, UV light)

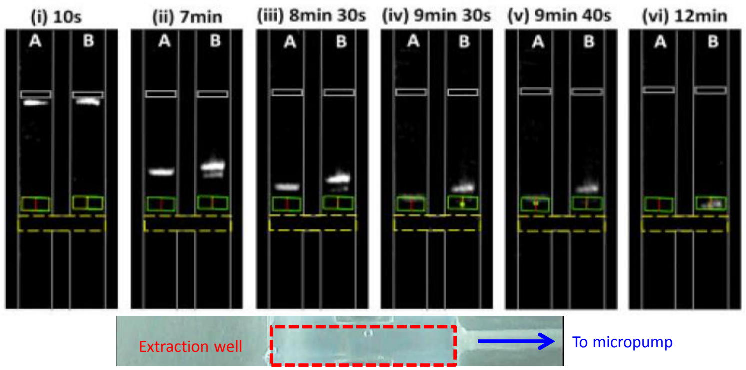
Chip design



[Step 3] Take out the final product

Multi-steps of DNA recombination into μ-fluidic chip

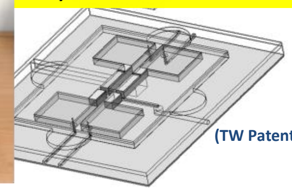
Demonstration



System overview

Microfluidic chip + Automatic control box

[Characteristics]
- Continuous electrophoresis & extraction
- Microfluidic mixing & control
- Precision thermal control of reaction
- Real-time image processing
- Fully automatic control
- Friendly user interface



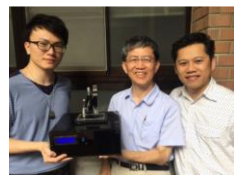
(TW Patent I358539)

Comparisons

	Traditional technique	Present LOC
Operation time	~1 day	< 1 hr
Amounts of DNA	3-5 mg	< 1 mg
Manual checkpoints	> 10	0
Gel cut	YES	NO
Gel extraction pack	YES	NO
Exposure to UV	~1 min/sample	NO
Multiple samples in parallel	Increase manpower	Easy by fully-automatic control
Manipulation of large DNA	Difficult	Feasible (> 10kb DNA vector)

Novel Biomedical Detection Easy & Fast Western Blotting by Thin-Film Direct Coating

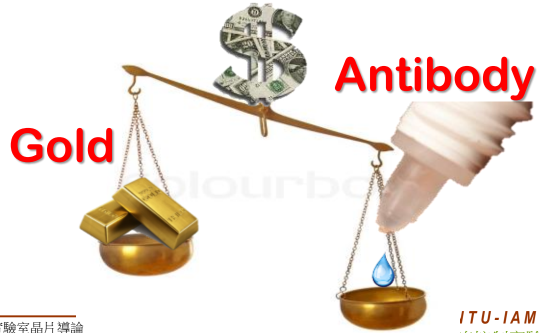
Analytical Chemistry, **86**, pp. 5164-5170, 2014
Analytical Chemistry, **88**, pp. 6349–6356, 2016.



The world smallest & lightest slot-die precision coating system

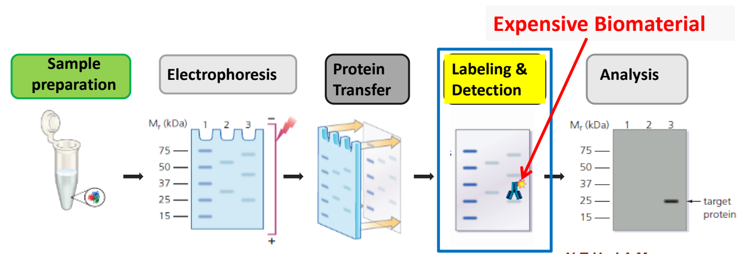
Characteristics of biomedical fluids

- generally **expensive** or even **limited**
- **Precision** is strictly needed

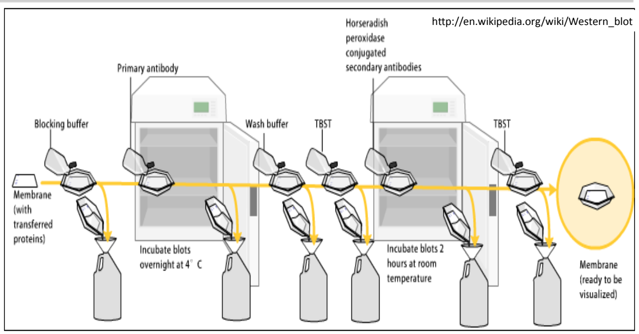


μ–fluidic -based Detection
Example: Western Blotting

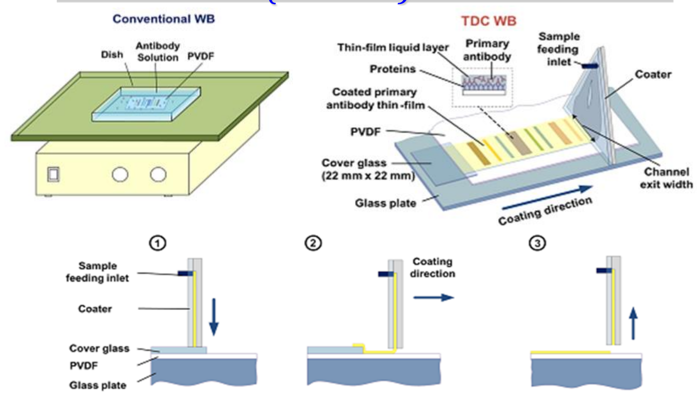
- Western blotting, also known as immunoblotting or protein blotting, is a core technique in cell and molecular biology
  - Detecting the presence of a specific protein in a complex mixture extracted from cells
  - Being widely used for the test of protein expression level



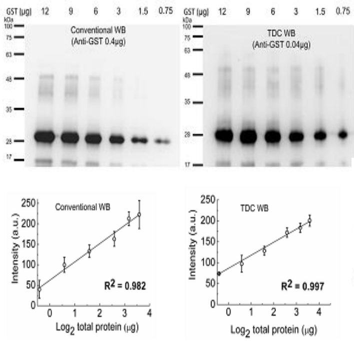
There are many tedious processes…



Thin-Film Direct Coating Western Blotting (TDC WB)

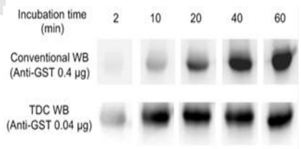


Performance Test of TDC WB



TDC WB vs. Conv. WB:

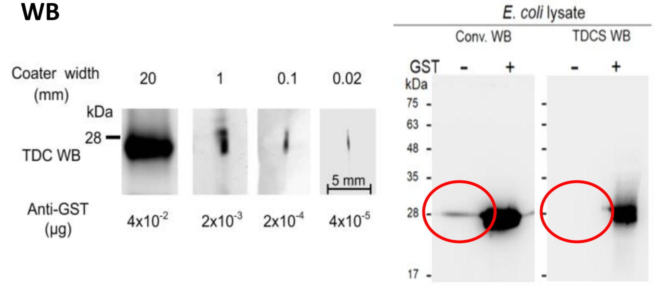
- **Better SNR**
- **less material needed**
- **Shorter time**



(Analytical Chemistry, 2014)

Performance Test of TDC WB

- **Reducing coating width of TDC WB**
- **Reducing false signal**



Performance Test of TDCS WB

- **By adding Suction after TDC coating (TDCS): material consumption: 1/100 ~ 1/10,000 operation time: 1/36**
- **Automatic platform**

	Convention WB	TDCS WB
Ab (μg)	2	0.02~0.0002
time(min)	180	≤ 5
Multi-Ab	No	Yes
SNR	good	excellent

(Analytical Chemistry, 2016)

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